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PHASE 2
PRELIMINARY ASSESSMENT OF THE RELATIVE TOXICITY
OF 1,5-DIAZIDO-3-NITRAZAPENTANE
90-DAY DERMAL APPLICATION MALE AND FEMALE RABBITS
STUDY NO. 75-51-Y809-90
MAY 1990 - JUNE 1992

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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT Distribution unlimited.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) 75-51-0809-92	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION U.S. Army Environmental Hygiene Agency 6b. OFFICE SYMBOL (*If applicable*) HSHB-MO-T	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (*City, State, and ZIP Code*) Aberdeen Proving Ground, MD 21010-5422	7b. ADDRESS (*City, State, and ZIP Code*)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Ballistics Research Laboratory 8b. OFFICE SYMBOL (*If applicable*) SLCBR-IB-P	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (*City, State, and ZIP Code*) Aberdeen Proving Ground, MD 21005	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. / PROJECT NO. / TASK NO. / WORK UNIT ACCESSION NO.

11. TITLE (*Include Security Classification*) Phase II, Preliminary Assessment of the Relative Toxicity of 1,5-Diazido-3-Nitrazapentane, 90-Day Dermal Application Male and Female Rabbits

12. PERSONAL AUTHOR(S)
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13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (*Year, Month, Day*)	15. PAGE COUNT
Final	FROM 5/90 TO 6/92	1992 June	43

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (*Continue on reverse if necessary and identify by block number*)
FIELD	GROUP	SUB-GROUP	1,5-Diazido-3-Nitrazapentane, Dermal, Approximate Lethal Dose (ALD), Testicular Hypospermatogenesis, Ovarian Follicle, No-observed-adverse-effect-level (NOAEL)

19. ABSTRACT (*Continue on reverse if necessary and identify by block number*)

A 90-day application of DANPE has the potential to cause testicular hypospermatogenesis in male rabbits and an apparent inhibition of mature ovarian follicles formation in female rabbits. A no-observed-adverse-effect-level was not achieved in the male rabbits but was achieved in female rabbits at 27.3 mg/kg dose level.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	UNCLASSIFIED
22a. NAME OF RESPONSIBLE INDIVIDUAL Everett A. Haight	22b TELEPHONE (*Include Area Code*) (410) 671-3980 DSN 584 22c. OFFICE SYMBOL HSHB-MO-T

DD Form 1473, JUN 86 *Previous editions are obsolete.*

SECURITY CLASSIFICATION OF THIS PAGE

UNCLASSIFIED

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO
ATTENTION OF

EXECUTIVE SUMMARY
PHASE 2
PRELIMINARY ASSESSMENT OF THE RELATIVE TOXICITY OF 1,5-DIAZIDO-3-NITRAZAPENTANE 90-DAY DERMAL APPLICATION MALE AND FEMALE RABBITS
STUDY NO. 75-51-Y809-90
MAY 1990 - JUNE 1992

1. GENERAL. A Preliminary Assessment of the Relative Toxicity of 1,5-Diazido-3-Nitrazapentane (DANPE) for a 90-day dermal application to male and female rabbits was completed in June 1992. The report is enclosed.

2. ESSENTIAL FINDINGS. A 90-day application of DANPE has the potential to cause testicular hypospermatogenesis in male rabbits and an apparent inhibition of mature ovarian follicle formation in female rabbits. A no-observed-adverse-effect level was not achieved in the male rabbits but was achieved in female rabbits at 27.3 mg/kg dose level.

3. RECOMMENDATIONS. The following paragraphs are recommendations based on professional scientific judgment:

a. Conduct further toxicological studies with DANPE in support of the requirement to provide data in establishing guidelines to the occupational health physician for safe workplace conditions.

b. Continue a short term chronic study with another rodent specie; the male and female rat.

c. Although DANPE poses no primary skin irritation, caution should be taken to prevent DANPE from being absorbed by the skin because of its potential to cause the forth mentioned problems in paragraph 2, above. Flush immediately with large volumes of water should skin contamination occur. Do not use abrasive soap, this may increase absorption through the skin.

d. Protective clothing should be worn by workers when contact is possible and splash guards in place to prevent splashing onto individuals or equipment being handled.

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO
ATTENTION OF

HSHB-MO-T

PHASE 2
PRELIMINARY ASSESSMENT OF THE RELATIVE TOXICITY OF 1,5-DIAZIDO-3-NITRAZAPENTANE 90-DAY DERMAL APPLICATION MALE AND FEMALE RABBITS STUDY NO. 75-51-Y809-90 MAY 1990 - JUNE 1992

1. REFERENCES. See Appendix A for a list of references.

2. AUTHORITY. Memorandum, 1st End, AMC, 31 Oct 88, AMCSG-I, subject: Toxicity Study.

3. PURPOSE. The subchronic study was designed to examine the toxic effects associated with continuous dermal exposure to 1,5-Diazido-3-Nitrazapentane (DANPE) over a period of 90 days. The results will provide information on possible target organs/ systems; establish a dose-response order of toxicity for DANPE and aid the occupational health physician in establishing preliminary guidelines for safe workplace conditions.

4. BACKGROUND.

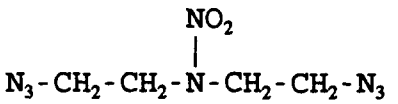
a. The DANPE (1,5-Diazido-3-Nitrazapentane), a flammable liquid, is of interest to the U.S. Army for use as an energetic material. No referenced toxicology information on this material was found in searches performed on the National Library of Medicine's Toxicology data network as listed in the Hazardous Substances Databank and in the Registry of Toxic Effects of Chemical Substances.

b. Previous evaluation of this compound in our Division suggests an oral approximate lethal dose (ALD) value in male rats 1,498 mg/kg and female rats 617 mg/kg. DANPE has a dermal toxicity of 3,192 mg/kg for female rabbits and 2,129 mg/kg in male rabbits. The DANPE has a primary eye irritant classification of "c," producing mild injury to the cornea. In addition, some injury to the conjuctiva was found. It has a skin irritant classification of "I," producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. The DANPE produced no sensitization reaction in guinea pigs (Reference 1).

5. MATERIALS.

a. The DANPE has a slightly irritating odor because of its solvent, ethyl acetate. The sample Lot #2316-C with a stated concentration of 37 percent DANPE was obtained from Naval Ordnance Station, Indian Head, Maryland. The batch sample was analyzed using the Digilab® FTS-15/90 Fourier Transform Infrared Spectrometer filtered with a Mercury-Cadmium-Telluride detector (Appendix B). The chemical structure of DANPE is as follows:

DANPE



b. Ethyl acetate is fairly nontoxic, and because of its characteristic fruity odor and pleasant taste when diluted, it is primarily used as fruit essences. Pertinent information regarding the mutagenicity, teratogenicity and carcinogenicity was not located in the Integrated Risk Information System.

c. This report, and data generated in these studies are stored in the Toxicology Division's files, which are located in the basement of Building 1570, Aberdeen Proving Grounds, Edgewood Area, MD 21010-5422.

d. Twenty-One-Day Range-Finding Dermal in the Rabbit.

*(1) This 21-day dermal study was performed in rabbits according to the Toxicology Division's Standing Operating Procedure (SOP) for 21-Day and Subchronic 90-Day Dermal Toxicity Studies (Reference 2).

(2) For this study, 60 rabbits, 30 male and 30 female were utilized. They were randomly selected into six groups of five male and female per group. Dosage groups were a fraction of the determined dermal approximate lethal dose (ALD) and an untreated control group (Table 1). The rabbits were between 3-6 months of age and 2.5-3.5 kgs in weight. This study was designed to permit the determination of the toxic effects associated with

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TABLE 1. PREDICTED DAILY DOSES (21-DAY DERMAL APPLICATION) DANPE

Group No.	Male Rabbits	Female Rabbits	Fraction of Dermal ALD
1	1250 Mg/Kg	1250 Mg/Kg	1/2x
2	312 Mg/Kg	312 Mg/Kg	1/4x
3	78 Mg/Kg	78 Mg/Kg	1/16x
4	20 Mg/Kg	20 Mg/Kg	1/64x
5	5 Mg/Kg	5 Mg/Kg	1/256x
6	Control (Untreated)	Control (Untreated)	---

repeated dermal exposure to DANPE and ethyl acetate over a limited period of time. The test provides information on target organs, possibilities of accumulation and effect/no-observed-adverse-effect levels.

(3) Dose levels for the five test groups of each sex were determined as fractions of the ALD values. Table 1 shows daily doses for the test. The day before dermal dosing, an area was shaved which intended dorsally from the base of the neck to pelvic girdle and laterally extending over the mid-lateral trunk. The calculated dose was applied unoccluded over the dorsal midline of the rabbits' back daily for 5 days per week for 3 weeks (15 doses over a 21-day test period). Individual animals' weight was determined prior to initial dosing, weekly, and at death. Weekly weights were used to calculate the delivered dosage to be applied for that week.

e. Ninety-Day Dermal.

*(1) This 90-day dermal study was performed in rabbits according to the Toxicology Division's SOP for 21-Day and Subchronic 90-Day Dermal Toxicity Studies (Reference 2).

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* Studies reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Care. In conducting the studies in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," U.S. Department of Health, Education and Welfare Publication No. (NIH) 86-23 revised 1985.

(2) For this study, 120 rabbits, 60 male and 60 female were obtained from Hazelton Research Products, Inc., Denver, Pennsylvania. The rabbits were between 3-6 months of age and 2.5-3.5 kgs in weight.

(3) Animals were randomly divided into 6 groups of 10 each male/female rabbits. Dosage levels were represented by a high, mid, and low-dose groups, a vehicle and cage control group and an additional recovery group. The day before dermal dosing, an area was shaved which intended dorsally from the base of the neck to the pelvic girdle and laterally extending over the mid-lateral trunk. The calculated dose was applied unoccluded over the dorsal midline of the rabbits' back daily for 5 days per week for a total of 13 weeks. Individual animals' weight was determined prior to initial dosing, weekly, and at death. Weekly weights were used to calculate the delivered dosage to be applied for that week.

(4) Dosage levels for the four test groups of each sex were determined from the 21-Day Dermal Application Range Finding Study. The high dose level (250 mg/kg) was the highest expected dosage that would not cause death. The lowest dose (25 mg/kg) was the highest dose expected to be the no observed adverse effect level (NOAEL). The middle dose level (50 mg/kg) was the lowest dose where any significant weight changes occurred. See Table 6 for Daily Doses.

(5) Animals to be bled for clinical and hematology analysis were randomly selected prior to dosing. There were pre- and post-exposure bleedings for comparison purposes.

TABLE 6. DAILY DOSES (MG/KG) - 90-DAY DERMAL APPLICATION

DANPE

Group No.	Male	Female
1	250	150
2	50	50
3	25	25
4	250 (Ethyl acetate) Solvent Control	250 (Ethly acetate)
5	Untreated Control	Untreated Control

(6) Appropriate action was taken to minimize the loss of animals during the study (e.g., refrigeration and necropsy of animals found dead, and sacrifice of weak or moribund animals with subsequent necropsy).

(7) On the final day of the study, blood samples were collected by the cephalic ear artery from both male and female rabbits each dose group. Tables 4 and 5 list the clinical chemistry and hematological parameters. After which, the rabbits were sacrificed and necropsied with appropriate histopathological examinations carried out.

TABLE 4. CLINICAL CHEMISTRY

Serum Glutamic Oxaloacetic Transaminase (Aspartate Aminotransferase)	(SGOT)	(AST)
Serum Glutamic Pyruvic Transaminase (Alanine Aminotransferase)	(SGPT)	(ALT)
Alkaline Phosphatase	(ALK.PHOS.)	
Glucose		
Blood Urea Nitrogen	(BUN)	
Total Protein		
Cholesterol		
Creatine Phosphokinase	(CPK)	
Triglycerides		
Total Bilirubin		
Lactic Dehydrogenase	(LDH)	
Prothrobin Times		

TABLE 5. HEMATOLOGY

Hematocrit
Hemoglobin
Erythrocyte Count
Total and Differential Leukocyte Counts
Mean Cell Volume
Mean Cell Hemoglobin
Mean Cell Hemoglobin Concentration

6. RESULTS.

a. Twenty-One-Day Dermal Application.

(1) All male and female rabbits in the two highest (1,250 and 312 mg/kg) dose groups died. The remaining four groups lost no animals. Tables 2 and 3 show the predicted verses actual daily doses each group received.

(2) Test data collected during this 21-day dermal application study (body weights, organ-to-body weight ratios, organ-to-body weight ratios, and blood chemistry values) were statistically compared with the data from their respective control groups using the student "t" test at the 0.05 level of significance (Appendices C-L).

(3) The clinical chemistry values (Appendices I and J) showed a significant change in total protein in the 78 mg/kg group for male rabbits and blood urea nitrogen in female rabbits of the same dose group when compared to their respective control groups. None of the other groups showed any significant differences.

(4) The blood hematology values revealed a decrease in the red blood cells, hemoglobin, and hematocrit for the male rabbits in the high dose group when compared to the control group. The white blood cells were increased (Appendix I). Female rabbits showed no significant changes from the control group (Appendix J).

(5) Significant decreases occurred in mean body weights for male rabbits receiving the high-dose compound (Appendix C).

(6) An increase in body weight-to-brain ratio was demonstrated in the male high dose (Appendix D) and the brain-to-organ weight ratio showed a decrease in the testes of the male low dose group when compared to the control group animals (Appendix E). The female rabbits showed now significant differences in any of the dose groups when compared with the control group animals (Appendices F and G).

b. Ninety-Day Dermal Application.

(1) Appendices O-W display a comparison of the predicted daily doses verses the actual daily doses for the 90-day dermal application study. Dosing in the highest groups of male and female rabbits was terminated at the 7th and 8th week (Appendices M and N) because the animals began dying. The investigators felt continuing dosing would result in death to all the animals.

TABLE 2. PREDICTED VERSES ACTUAL DAILY DOSES (21-DAY DERMAL APPLICATION)

DANPE (MALE RABBITS)

	Week I (Mg/Kg)	Week II (Mg/Kg)	Week III (Mg/Kg)
		GROUP I	
Predicted	1250	1250	1250
Actual	1717	*___	*___
		GROUP II	
Predicted	312	312	312
Actual	427	509	529
		GROUP III	
Predicted	78	78	78
Actual	106.2	128.4	140.5
		GROUP IV	
Predicted	20	20	20
Actual	31.6	35.9	35.6
		GROUP V	
Predicted	5	5	5
Actual	6.8	7.8	8.3
		GROUP VI (Control)	
Predicted	0	0	0
Actual	0	0	0

* All Animals Died.

Phase 2, Toxicological Study No. 75-51-Y809-90, May 90 - Jun 92

TABLE 3. PREDICTED VERSES ACTUAL DAILY DOSES (21-DAY DERMAL APPLICATION)

DANPE (FEMALE RABBITS)

	Week I (Mg/Kg)	Week II (Mg/Kg)	Week III (Mg/Kg)
		GROUP I	
Predicted	1250	1250	1250
Actual	1837	*	*
		GROUP II	
Predicted	312	312	312
Actual	475	519	*
		GROUP III	
Predicted	78	78	78
Actual	108	133.2	128.8
		GROUP IV	
Predicted	20	20	20
Actual	27.4	33.8	34.1
		GROUP V	
Predicted	5	5	5
Actual	6.8	8.3	8.7
		GROUP VI (Control)	
Predicted	0	0	0
Actual	0	0	0

* All Animals Died.

(2) Test data collected during this 90-Day dermal application study (body weights, organ-to-body weight ratios, organ-to-body weight ratios, and blood chemistry values) were statistically compared with the data from their respective control groups using the student "t" test at the 0.05 level of significance (Appendices O, P, Q, and R).

(3) Blood clinical chemistry values (Appendices S and T) demonstrated no significant changes when compared to their respective control groups.

(4) The blood hematology values revealed a decrease in red blood cells, hemoglobin, and hematocrit for both male and female rabbits in the high dose group (Appendices U and V).

(5) Dose-related significant increases were noted in body-to-organ weight ratios (Appendices Q-X). High dosed (150 mg/kg) female rabbits showed significant increases in liver, kidney, heart, ovaries (Figure 1) and brain weight ratios. High dose (250 mg/kg) male rabbits showed significance in heart, kidney, testes (Figure 2), and brain weight ratios. The mid-dose (50 mg/kg) group of female rabbits showed significance in kidney, ovaries, and brain weight ratios. The mid-dose (50 mg/kg) group of male rabbits showed significance testes and brain weight ratios. The only significance noted in the low dose (25 mg/kg) group was in the testes of the male rabbits. These results were demonstrated when compared to the control animal group organ and body weight.

(6) Dermal application of DANPE in rabbits was associated with a high incidence of testicular hypospermatogenesis in animals that received 50 or 250 mg/kg of the test material. A lower incidence of similar testicular changes were noted in rabbits that received 25 mg/kg of the test material. The testicular change was present in animals that died or were sacrificed during the course of the study. Testicular hypospermatogenesis was not observed in the untreated control males or males that received 250 mg/kg ethyl acetate. There was an apparent compound-related inhibition of ovarian follicle formation that was noted in all females that received 50 or 150 mg/kg of the test material and survived to the terminal sacrifice. Presence of mature follicles in females that received 150 mg/kg and died 2-6 weeks into the study, suggests DANPE administration for that duration did not interfere with follicle formation. Female and male rabbits receiving 150 and 250 mg/kg DANPE had a low incidence of focal or multifocal demyelinization in the midbrain. There was also a low incidence of inflammatory lesions in the lungs, suggesting nonspecific pulmonary irritation associated with the DANPE treatment. The DANPE-treated rabbits had a low incidence of lesions in the tongue, esophagus, and stomach that suggested ingestion of the test material, possibly

Ovary Weights (Danpe)
Female Rabbits 90-Day Dermal

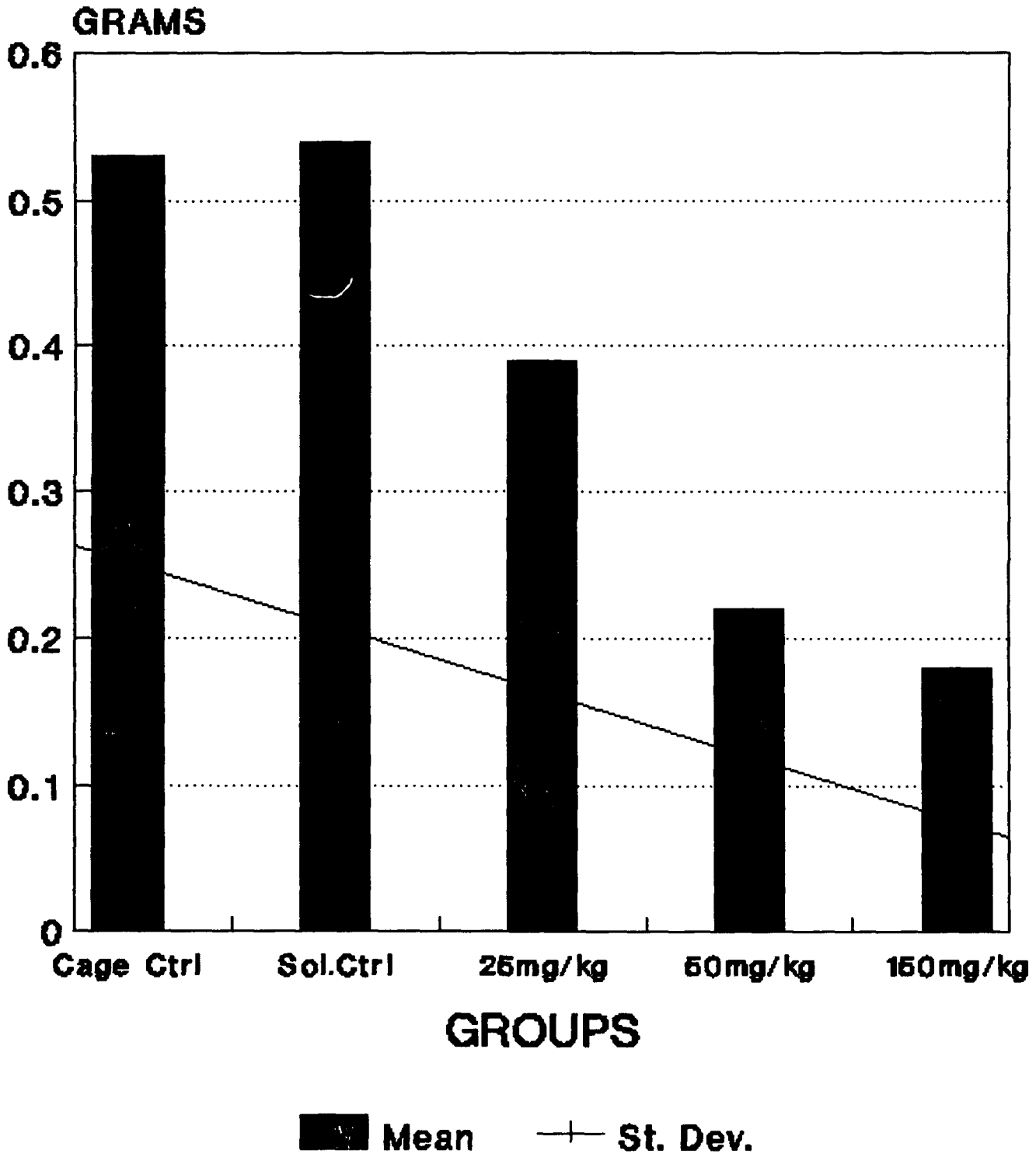

Figure 1.

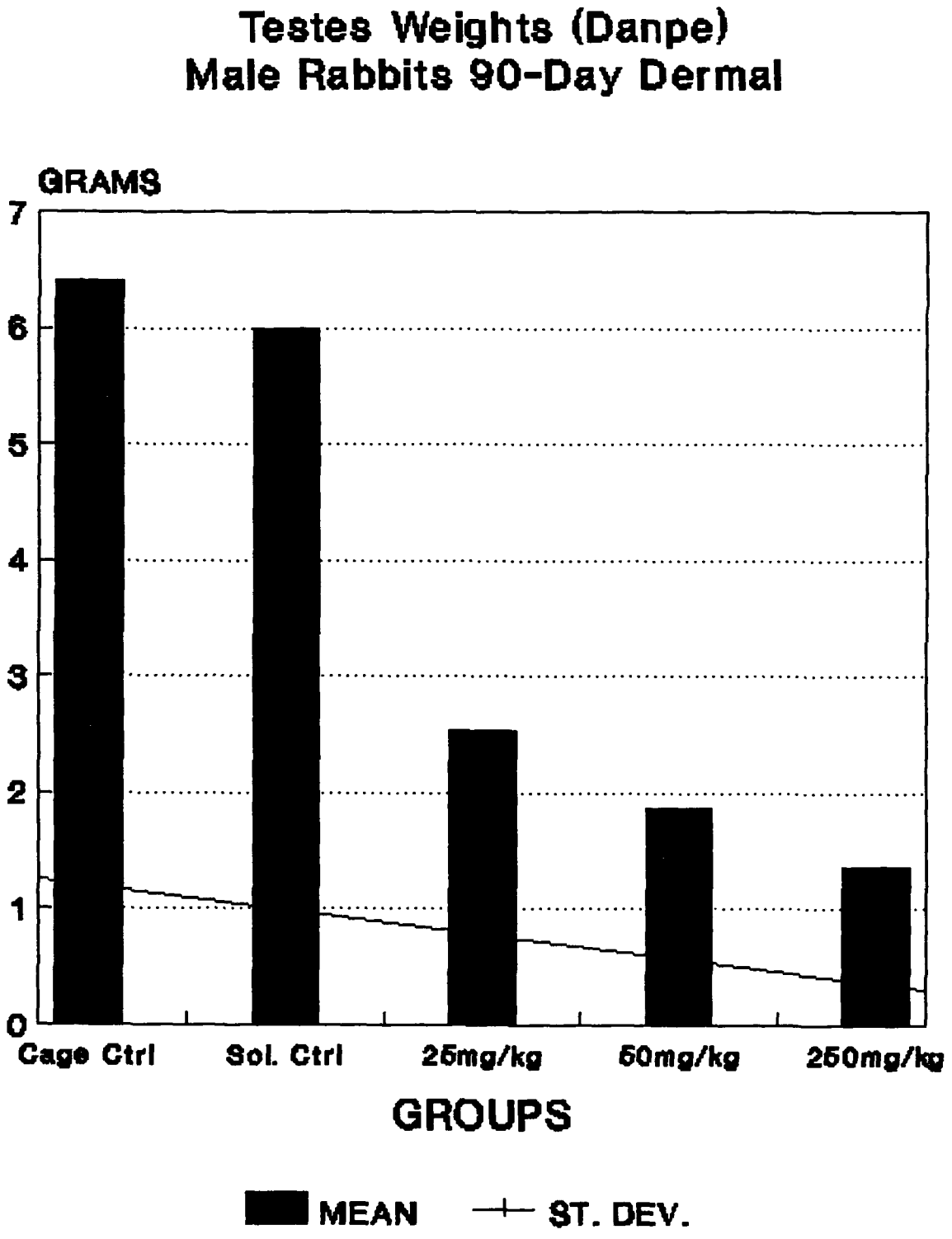
Testes Weights (Danpe)
Male Rabbits 90-Day Dermal
GRAMS
7
6
5
4
3
2
1
0
Cage Ctrl
Sol. Ctrl
25mg/kg
50mg/kg
250mg/kg
GROUPS
MEAN
ST. DEV.

Figure 2.

from licking the application area. There was an increase in the incidence of sequestered blood in the lymph nodes of DANPE-treated animals (male and female), suggesting hemorrhage in the region served by the lymph node (reference 3).

7. DISCUSSION.

a. The results of the 21-day short term and 90-day subchronic dermal application of Danpe studies indicate this compound causes testicular hypospermatogenesis in the male and the inhibition of mature ovarian follicles in female rabbits (reference 3).

b. Although the clinical chemistry values revealed no significant changes, the hematology blood work showed in the high dose group for male and female rabbits a decrease in red blood cells, hemoglobin and hematocrit values. This could possibly be associated with the incidence of sequestered blood in the lymph nodes, suggesting hemorrhage (reference 3).

c. A review of the results from these studies suggest a NOAEL was not achieved in the male rabbits but achieved in the female rabbits at the 27.3 mg/kg dose level.

8. RECOMMENDATIONS.

a. Continue a short term chronic study with another rodent specie; the male and female rat.

b. Use extreme caution to prevent DANPE from skin contact. Flush immediately with large volumes of water should skin contamination occur. Do not use abrasive soap because this may increase absorption through the skin.

c. Wear protective clothing when contact is possible and keep splash guards in place to prevent splashing onto individuals or equipment that is being used.

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APPENDIX A

REFERENCES

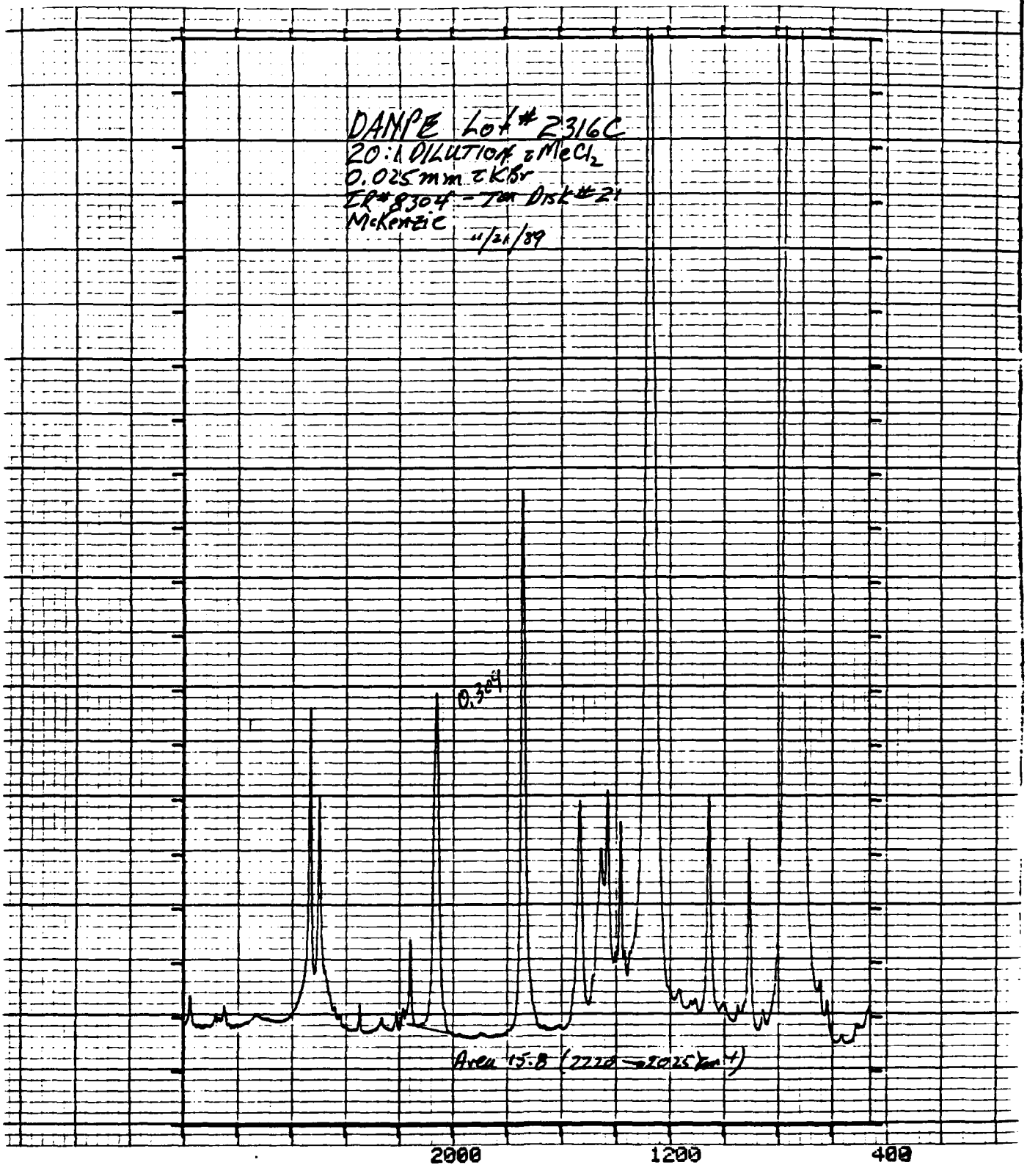
1. Phase 1, Preliminary Assessment of the Relative Toxicity of 1,5-Diazido-3-Nitrazapentane (DANPE) Acute Toxicity, Study No. 75-51-0856-91, February 1992.

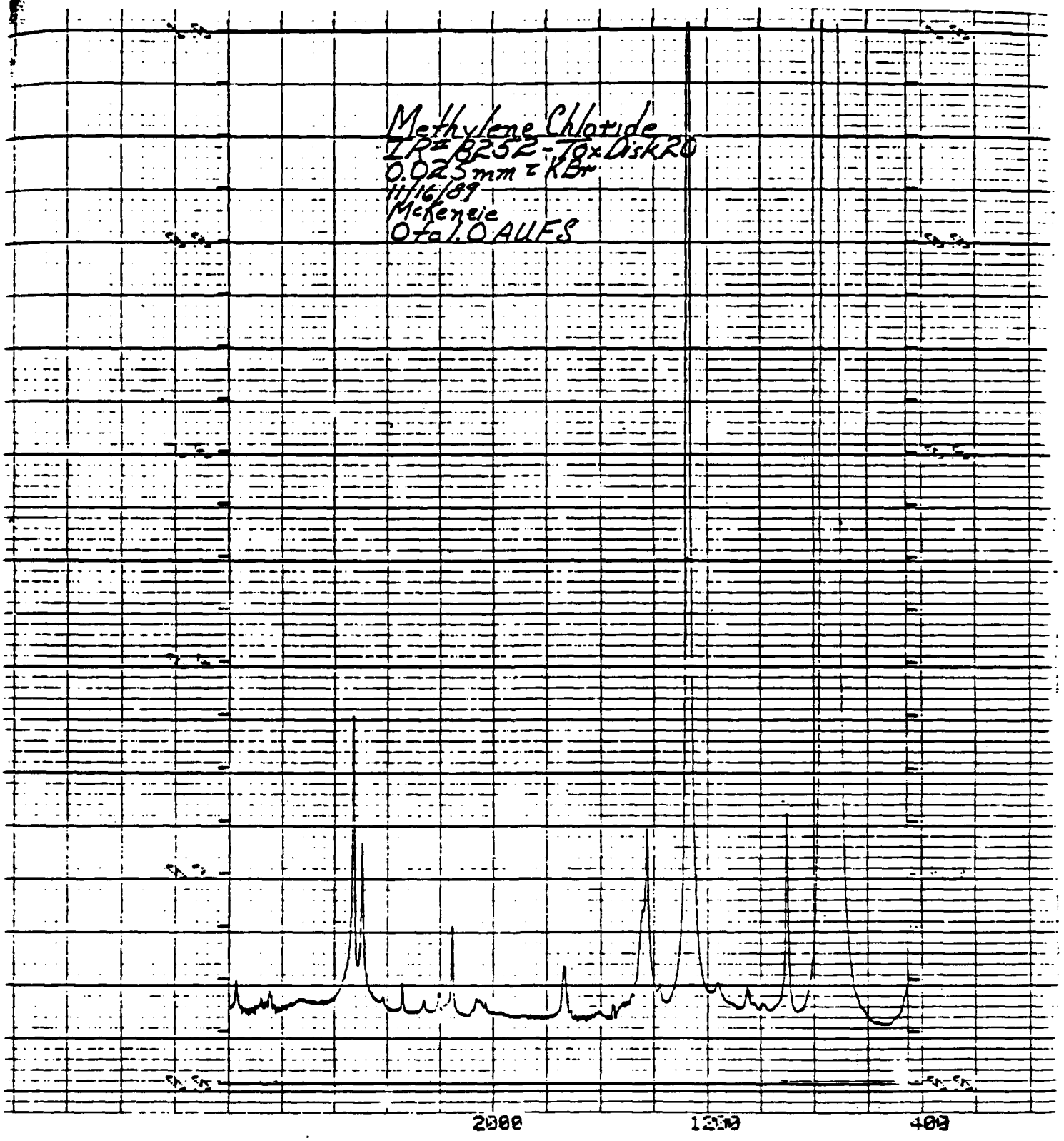
2. Standing Operating Procedure No. 32, HSHB-MO-T, 24 February 1990, subject: 21-Day Range Finding and Subchronic 90-Day Dermal Toxicity Study.

3. Report: 13 March 1991, George A. Parker, DVM, 111-A Carpenter Drive, P.O. Box 764, Sterling, VA 22120, subject: Final Pathology Report, 1,5-Diazido-3-Nitrazapentane (DANPE) 90-Day Dermal Study in Male and Female Rabbits, Study No. 75-51-0856-89.

APPENDIX B

SPECTRA DIAGRAM OF DANPE LOT NO. 2316C


DAMPE Lot# 2316C
20:1 DILUTION in $MeCl_2$
0.025 mm in KBr
ER#8304 - Ten Disk #21
McKenzie
11/21/89
0.30
Area 15.8 (7220 - 2025 cm⁻¹)
2000
1200
400



Reference Material Spectra

APPENDIX C

RABBIT 21-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
MALE

TERMINAL WEIGHTS (GMS)

Dosage Predicted (Actual)	78 Mg/Kg (125)	20 Mg/Kg (34.4)	5 Mg/Kg (7.6)	Cage Cont (0)
Liver	113.5 +-22.69	122.5 +-22.39	114.4 +-18.51	119.6 +-7.28
Kidney	17.09 +-2.54	19.42 +-4.09	18.68 +-2.04	19.7 +-2.57
Spleen	1.62 +-0.53	1.76 +-1.11	1.76 +-0.50	2.16 +-1.61
Heart	5.86 +-0.77	7.14 +-0.30	7.14 +-1.05	7.78 +-2.22
Testes	3.88 +-1.60	3.62 +-0.16	3.42 +-0.51	4.02 +-0.41
Adrenal	0.31 +-0.06	0.23 +-0.05	0.31 +-0.04	0.26 +-0.07
Brain	9.82 +-0.54	9.46 +-0.30	10.1 +-0.56	9.36 +-0.47
Body Wts	2.32 *+-0.26	2.92 +-0.33	3.03 +-0.26	3.00 +-0.25

* Significantly different from control at the 0.05 level of probability.

APPENDIX D

RABBIT 21-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
MALE ORGAN TO BODY WEIGHT RATIOS

% OF BODY WEIGHT

Dosage Predicted (Actual)	78 Mg/Kg (125)	20 Mg/Kg (34.4)	5 Mg/Kg (7.6)	Cage Cont (0)
Liver	4.35 +-0.90	4.17 +-0.35	3.72 +-0.41	3.99 +-0.31
Kidney	0.65 +-0.09	0.66 +-0.12	0.62 +-0.04	0.66 +-0.09
Spleen	0.06 +-0.02	0.06 +-0.04	0.06 +-0.01	0.07 +-0.05
Heart	0.22 +-0.01	0.25 +-0.03	0.23 +-0.02	0.26 +-0.06
Testes	0.15 +-0.06	0.13 +-0.01	0.12 +-0.01	0.13 +-0.02
Brain	0.38 *+-0.03	0.33 +-0.03	0.34 +-0.03	0.32 +-0.03
Adrenals	0.01 +-0.00	0.01 +-0.00	0.01 +-0.00	0.01 +-0.00

* Significantly different from control at the 0.05 level of probability.

APPENDIX E

RABBIT 21-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
MALE ORGAN TO BRAIN WEIGHT RATIOS (GMS)

% OF BRAIN WEIGHT

Dosage Predicted (Actual)	78 Mg/Kg (125)	20 Mg/Kg (34.4)	5 Mg/Kg (7.6)	Cage Cont (0)
Liver	1158.76 +-239.13	1294.77 +-234.71	1134.98 +-184.67	1281.64 +-121.56
Kidney	173.88 +-22.27	205.26 +-43.13	185.10 +-19.67	210.49 +-26.56
Spleen	16.38 +-4.73	18.54 +-11.60	17.32 +-4.34	22.71 +-15.74
Heart	59.54 +-5.25	75.57 +-4.64	70.77 +-10.00	82.72 +-21.36
Testes	39.67 +-17.02	38.31 +-2.54	33.78 *+-4.11	42.89 +-2.73
Adrenal	3.18 +-0.66	2.48 +-0.60	3.04 +-0.46	2.75 +-0.82

* Significantly different from control at the 0.05 level of probability.

APPENDIX F

RABBIT 21-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
FEMALE

TERMINAL WEIGHTS (GMS)

Dosage Predicted (Actual)	78 Mg/Kg (125)	20 Mg/Kg (34.4)	5 Mg/Kg (7.6)	Cage Cont (0)
Liver	103.5 +-15.2	100.4 +-18.69	127.6 +-41.00	117.2 +-35.6
Kidney	15.4 +-1.40	15.1 +-1.97	20.3 +-2.8	17.6 +-1.96
Spleen	1.14 +-0.31	1.56 +-0.52	2.66 +-1.62	1.48 +-0.55
Heart	5.95 +-0.83	5.84 +-1.19	7.00 +-1.09	6.25 +-0.75
Ovaries	0.18 +-0.01	0.29 +-0.15	0.22 +-0.07	0.27 +-0.08
Adrenal	0.30 +-0.07	0.31 +-0.07	0.35 +-0.10	0.25 +-0.02
Brain	9.70 +-0.39	9.78 +-0.50	9.34 +-0.32	9.75 +-0.31
Body Wts	2.78 +-0.18	2.73 +-0.35	3.11 +-0.24	3.08 +-0.17

APPENDIX G

RABBIT 21-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
FEMALE ORGAN TO BODY WEIGHT RATIOS

% OF BODY WEIGHT

Dosage Predicted (Actual)	78 Mg/Kg (125)	20 Mg/Kg (34.4)	5 Mg/Kg (7.6)	Cage Cont (0)
Liver	3.71 +-0.33	3.66 +-0.33	4.10 +-1.25	3.78 +-0.97
Kidney	0.56 +-0.04	0.56 +-0.13	0.65 +-0.06	0.57 +-0.05
Spleen	0.04 +-0.01	0.06 +-0.02	0.08 +-0.05	0.05 +-0.02
Heart	0.22 +-0.02	0.22 +-0.06	0.23 +-0.03	0.20 +-0.02
Ovaries	0.01 +-0.00	0.01 +-0.01	0.01 +-0.003	0.01 +-0.00
Brain	0.35 +-0.02	0.36 +-0.07	0.30 +-0.03	0.32 +-0.02
Adrenals	0.01 +-0.00	0.01 +-0.00	0.01 +-0.00	0.01 +-0.00

APPENDIX H

RABBIT 21-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
FEMALE ORGAN TO BRAIN WEIGHT RATIOS (GMS)

% OF BRAIN WEIGHT

Dosage Predicted (Actual)	78 Mg/Kg (125)	20 Mg/Kg (34.4)	5 Mg/Kg (7.6)	Cage Cont (0)
Liver	1066.53 +-148.75	1032.43 +-218.24	1360.63 +-397.11	1199.02 +-347.79
Kidney	158.53 +-8.69	154.07 +-18.95	217.11 +-30.79	180.84 +-19.79
Spleen	11.77 +-3.35	16.13 +-5.71	28.80 +-18.31	15.14 +-5.32
Heart	61.18 +-6.63	59.94 +-13.01	75.22 +-13.71	64.01 +-6.31
Ovaries	1.85 +-0.12	3.01 +-1.71	2.38 +-0.74	2.72 +-0.78
Adrenal	3.07 +-0.72	3.20 +-0.90	3.74 +-1.03	2.54 +-0.28

APPENDIX I

21-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
CLINICAL CHEMISTRY - MALE RABBITS

Dosage Predicted (Actual)	Alk. Phos IU/L	SGOT IU/L	SGPT IU/L	Glucose IU/L	T. Bili Mg/DL	Bun Mg/DL	Tot. LDH IU/L	Tot. Prot G/DL	Cholesterol IU/L	Calcium Mg/DL	CPK IU/L	Triglycerides IU/L
78 Mg/Kg (125)	86.66 +-25.65	11.81 +-3.80	27.34 +-8.91	140.36 +-10.07	0.22 +-0.04	18.39 +-2.96	66.74 +-27.75	5.96 *+-0.23	53.47 +-19.93	16.48 +-1.27	314.10 +-100.30	103.80 +-16.72
20 Mg/Kg (34.4)	111.86 +-28.73	12.07 +-4.30	24.60 +-3.61	140.04 +-14.32	0.24 +-0.07	18.07 +-3.46	50.90 +-15.14	6.10 +-0.26	36.38 +-12.22	15.75 +-1.17	396.50 +-67.28	94.47 +-19.22
5 Mg/Kg (7.6)	142.48 +-24.39	11.76 +-3.05	36.93 +-8.12	142.00 +-5.49	0.22 +-0.05	16.25 +-3.36	59.32 +-28.35	6.07 +-0.39	43.34 +-14.84	16.49 +-2.30	371.62 +-54.33	100.82 +-9.37
Control	148.40 +-56.84	12.33 +-4.26	26.31 +-7.86	148.04 +-20.27	0.26 +-0.06	20.28 +-2.33	55.11 +-19.85	6.41 +-0.28	36.64 +-11.72	16.23 +-1.44	466.69 +-112.72	144.69 +-59.55

Alk.Phos - Alkaline Phosphatase
SGOT - Serum Glutamic Oxaloacetic Transaminase
SGPT - Serum Glutamic Pyruvic Transaminase
Glucose
T. Bili - Total Bilirubin
Bun - Blood Urea Nitrogen
Tot. LDH - Total Lactic Dehydrogenase
Tot. Prot. - Total Protein
Cholesterol
CPK - Creatine Phosphokinase
Triglycerides
CA - Calcium

APPENDIX J

21-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
CLINICAL CHEMISTRY - FEMALE RABBITS

Dosage Predicted (Actual)	Alk.Phos IU/L	SGOT IU/L	SGPT IU/L	Glucose IU/L	T.Bili Mg/DL	Bun IU/L	Tot.LDH IU/L	Tot.Prot. G/DL	Cholesterol IU/L	CPK IU/L	Triglycerides IU/L
78 Mg/Kg (125)	176.63 +-124.46	12.18 +-4.09	32.24 +-9.01	146.42 +-8.53	0.27 +-0.02	19.125 *+-1.00	38.08 +-8.81	5.47 +-0.21	95.36 +-35.63	341.30 +-63.36	97.11 +-43.77
20 Mg/Kg (34.4)	124.18 +-55.61	12.79 +-3.14	29.40 +-6.35	150.88 +-17.96	0.25 +-0.04	19.92 +-5.02	57.31 +-9.70	5.64 +-0.24	87.39 +-36.69	457.04 +-63.01	97.41 +-38.24
5 Mg/Kg (7.6)	137.64 +-38.05	12.33 +-3.14	26.10 +-11.45	157.26 +-36.23	0.24 +-0.02	23.76 +-4.38	44.69 +-5.78	5.95 +-0.56	62.59 +-8.57	456.34 +-195.72	87.96 +-45.55
Control	139.32 +-21.95	14.18 +-6.40	32.50 +-12.65	160.35 +-20.63	0.24 +-0.02	23.96 +-1.15	46.59 +-0.45	5.83 +-10.41	52.27 +-112.87	327.02 +-34.18	80.25

* Statistical significance at the p >0.05 level.

Alk.Phos - Alkaline Phosphatase
SGOT - Serum Glutamic Oxaloacetic Transaminase
SGPT - Serum Glutamic Pyruvic Transaminase
Glucose
T. Bili - Total Bilirubin
Bun - Blood Urea Nitrogen
Tot. LDH - Total Lactic Dehydrogenase
Tot. Prot. - Total Protein
Cholesterol
CPK - Creatine Phosphokinase
Triglycerides

APPENDIX K

21-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
HEMATOLOGY - MALE RABBITS

Dosage Predicted (Actual)	RBC 10/µL	HCT %	MCV fl	WBC 10/µL	HGB g/dl	MCH pg	MCHC g/dl	Heterophiles %	Lymphocytes %	Monocytes %
78 Mg/Kg (125)	5.14 *+-0.76	33.90 *+-4.42	66.20 +-1.75	12.40 *+-3.06	11.60 *+-1.48	22.60 +-0.76	34.20 +-0.24	40.60 +-20.07	58.20 +-20.30	1.50 +-0.58
20 Mg/Kg (34.4)	6.16 +-0.58	40.60 +-3.09	66.00 +-2.89	9.80 +-2.4	13.80 +-0.98	22.40 +-1.10	34.00 +-0.27	39.00 +-15.21	59.80 +-14.91	1.20 +-0.45
5 Mg/Kg (7.6)	6.02 +-0.40	39.80 +-2.51	66.10 +-2.59	10.90 +-4.05	13.50 +-0.83	22.50 +-0.99	34.00 +-0.27	28.20 +-13.63	71.40 +-13.45	1.50 +-0.58
Control	6.04 +-0.34	40.90 +-2.71	67.80 +-3.27	8.90 +-1.73	13.90 +-1.01	23.00 +-1.04	33.90 +-0.51	37.20 +-7.69	61.60 +-7.80	1.50 +-0.58

* Statistical significance at the p >0.05 level.

RBC - Red Blood Cells
HGB - Hemoglobin
HCT - Hematocrit
MCV - Mean Cell Volume
MCH - Mean Cell Hemoglobin
MCHC - Mean Cell Hemoglobin Concentration
WBC - White Blood Cell

APPENDIX L
21-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
HEMATOLOGY - FEMALE RABBITS

Dosage Predicted (Actual)	RBC 10/µL	HCT %	MCV fl	WBC 10/µL	HGB g/dl	MCH pg	MCHC g/dl	Heterophiles %	Lymphocytes %	Monocytes %
78 Mg/Kg (125)	5.77 +-0.61	36.90 +-2.16	64.20 +-3.02	10.00 +-1.20	12.50 +-0.66	21.80 +-1.25	34.00 +-0.66	31.00 +-10.10	67.75 +-10.31	1.25 +-0.50
20 Mg/Kg (34.4)	5.78 +-0.78	37.00 +-4.05	64.30 +-2.00	11.60 +-2.50	12.50 +-1.56	21.60 +-0.49	33.60 +-0.75	36.20 +-8.40	62.80 +-8.07	1.25 +-0.50
5 Mg/Kg (7.6)	5.44 +-0.23	36.20 +-1.39	66.60 +-1.34	9.30 +-0.89	12.10 +-0.41	22.30 +-0.58	33.50 +-0.26	34.20 +-16.89	64.40 +-17.27	1.40 +-0.55
Control	5.75 +-0.33	38.40 +-1.14	66.80 +-1.96	8.40 +-2.13	13.10 +-0.39	22.80 +-0.84	34.10 +-0.35	40.25 +-12.04	58.50 +-12.26	1.25 +-0.50

RBC - Red Blood Cells
HGB - Hemoglobin
HCT - Hematocrit
MCV - Mean Cell Volume
MCH - Mean Cell Hemoglobin
MCHC - Mean Cell Hemoglobin Concentration
WBC - White Blood Cell

APPENDIX M

RABBIT 90-DAY DERMAL
DANPE DOSAGES
STUDY NO. 75-51-0809-91
MALE

Dosage	Total Mean Ave.	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Predicted	(250 Mg/Kg)	250	250	250	250	250	250
Actual	(263.1 Mg/Kg)	274	271.2	256.4	268	256.9	264.8
Predicted	(50 Mg/Kg)	50	50	50	50	50	50
Actual	(48.3 Mg/Kg)	52.7	52.3	48.8	52.9	55.8	55.9
Predicted	(25 Mg/Kg)	25	25	25	25	25	25
Actual	(24.9 Mg/Kg)	30.4	31.6	28.8	28	26.5	26.4
Control	(0 Mg/Kg)	0	0	0	0	0	0

Dosage	Total Mean Ave.	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13
Predicted	(250 Mg/Kg)	250	250	250	250	250	250	250
Actual	(263.1 Mg/Kg)	---*	---*	---*	---*	---*	---*	---*
Predicted	(50 Mg/Kg)	50	50	50	50	50	50	50
Actual	(48.3 Mg/Kg)	52.8	50.2	46.7	46.7	50.8	50.0	58.6
Predicted	(25 Mg/Kg)	25	25	25	25	25	25	25
Actual	(24.9 Mg/Kg)	25.6	25	21.9	22.7	25.3	24.6	29.3
Control	(0 Mg/Kg)	0	0	0	0	0	0	0

* High dose animals stopped dosing.

APPENDIX N

RABBIT 90-DAY DERMAL APPLICATION
DANPE DOSAGES
STUDY NO. 75-51-0809-91
FEMALE

Dosage	Total Mean Ave.	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Predicted	(150 Mg/Kg)	150	150	150	150	150	150
Actual	(158.9 Mg/Kg)	149.7	153.9	161.6	159.6	161	167.6
Predicted	(50 Mg/Kg)	50	50	50	50	50	50
Actual	(53.4 Mg/Kg)	49	60.2	53.5	51.4	48	53.7
Predicted	(25 Mg/Kg)	25	25	25	25	25	25
Actual	(27.3 Mg/Kg)	29	32.4	28.1	26.2	25	26.3
Control	(0 Mg/Kg)	0	0	0	0	0	0

Dosage	Total Mean Ave.	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13
Predicted	(150 Mg/Kg)	150	150	150	150	150	150	150
Actual	(158.9 Mg/Kg)	---*	---*	---*	---*	---*	---*	---*
Predicted	(50 Mg/Kg)	50	50	50	50	50	50	50
Actual	(53.4 Mg/Kg)	59.2	52.7	54.2	53	48.1	52.9	57.9
Predicted	(25 Mg/Kg)	25	25	25	25	25	25	25
Actual	(27.3 Mg/Kg)	30.6	26.1	27.2	27.1	24.3	24.7	27.7
Control	(0 Mg/Kg)	0	0	0	0	0	0	0

* High dose animals stopped dosing.

APPENDIX O

RABBIT 90-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
FEMALE

TERMINAL WEIGHTS (GMS)

Dosage Predicted (Actual)	150 Mg/Kg (158.9)	50 Mg/Kg (53.4)	25 Mg/Kg (27.3)	Ethylacetate (250)	Cage Cont (0)
Liver	131.17 +-23.76	112.53 +-20.27	132.46 +-36.61	134.28 +-40.60	123.35 +-25.13
Kidney	19.75 +-2.16	18.46 +-2.23	19.18 +-2.49	21.38 +-4.36	18.81 +-1.88
Spleen	1.48 +-0.79	1.74 +-0.88	1.83 +-0.38	1.75 +-0.75	1.76 +-0.61
Heart	7.88 +-1.65	6.98 +-1.05	7.82 +-1.42	8.19 +-1.53	7.82 +-0.84
Ovaries	0.18 *+-0.06	0.22 *+-0.10	0.39 +-0.26	0.54 +-0.14	0.53 +-0.26
Adrenal	0.40 +-0.07	0.34 +-0.09	0.40 +-0.07	0.45 +-0.11	0.41 +-0.07
Brain	9.98 +-0.42	9.78 +-0.83	9.89 +-0.42	9.46 +-0.53	9.62 +-0.50
Body Wts (Kgs)	3.73 *+-0.50	3.71 *+-0.69	4.17 +-0.54	4.57 +-0.66	4.32 +-0.38

* Significantly different from control at the 0.05 level of probability.

APPENDIX P

RABBIT 90-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
FEMALE BODY TO ORGAN WEIGHT RATIOS

% BODY WEIGHT

Dosage Predicted (Actual)	150 Mg/Kg (158.9)	50 Mg/Kg (53.4)	25 Mg/Kg (27.3)	Ethylacetate (250)	Cage Co (0)
Liver	3.51 *+-0.43	3.07 +-0.42	3.14 +-0.48	2.90 +-0.61	2.86 +-0.56
Kidney	0.53 *+-0.05	0.51 *+-0.09	0.46 +-0.03	0.47 +-0.06	0.44 +-0.03
Heart	0.21 *+-0.02	0.19 +-0.03	0.19 +-0.02	0.18 +-0.02	0.18 +-0.02
Spleen	0.04 +-0.02	0.05 +-0.04	0.04 +-0.01	0.04 +-0.01	0.04 +-0.01
Ovaries	0.01 *+-0.0036	0.01 *+-0.0030	0.01 +-0.01	0.01 +-0.0036	0.01 +-0.01
Brain	0.27 *+-0.03	0.27 *+-0.06	0.24 +-0.03	0.21 +-0.04	0.23 +-0.02

* Significantly different from control at the 0.05 level of probability.

APPENDIX Q

RABBIT 90-DAY DERMAL
DANPE
STUDY NO. 75-51-0809-91
MALE BRAIN TO ORGAN WEIGHT RATIOS

% OF BRAIN WEIGHT

Dosage Predicted (Actual)	250 Mg/Kg (263.1)	50 Mg/Kg (48.3)	25 Mg/Kg (24.9)	Ethylacetate (250)	Cage Cont (0)
Liver	1100.81 +-235.65	1134.39 +-213.77	1344.55 +-309.14	1450.37 *+-215.54	1224.89 +-175.60
Kidney	190.43 +-25.64	193.66 +-43.71	202.62 +-35.21	217.41 *+-39.84	184.62 +-8.50
Spleen	13.43 +-4.12	12.60 +-2.67	14.26 +-4.73	13.15 +-3.43	16.23 +-5.08
Testes	14.23 *+-4.03	18.66 *+-4.80	25.78 *+-9.46	62.02 +-9.14	63.36 +-10.86
Heart	84.45 +-14.11	82.88 +-12.31	95.59 +-16.96	102.16 *+-11.79	86.23 +-8.09
Adrenal	3.72 +-0.42	3.27 +-1.26	3.68 +-0.79	3.94 +-1.51	3.79 +-1.21

* Significantly different from control at the 0.05 level of probability.

APPENDIX R

RABBIT 90-DAY DERMAL
DANPE
STUDY NO. 75-51-0809-91
MALE

TERMINAL WEIGHTS (GMS)

Dosage Predicted (Actual)	250 Mg/Kg (263.1)	50 Mg/Kg (48.3)	25 Mg/Kg (24.9)	Ethylacetate (250)	Cage Cont (0)
Liver	106.68 +-22.37	114.76 +-27.46	132.88 +-28.30	139.75 +-18.17	123.7 +-18.23
Kidney	18.37 +-2.23	19.53 +-4.80	20.03 +-3.09	20.91 +-3.26	18.65 +-1.23
Spleen	1.31 +-0.43	1.27 +-0.31	1.43 +-0.52	1.28 +-0.37	1.64 +-0.53
Testes	1.37 *+-0.38	1.87 *+-0.47	2.53 *+-0.86	6.00 +-0.96	6.41 +-1.20
Brain	9.67 *+-0.39	10.05 +-0.62	9.92 +-0.43	9.69 +-0.73	10.10 +-0.40
Adrenals	0.36 +-0.05	0.38 +-0.11	0.36 +-0.07	0.40 +-0.13	0.38 +-0.12
Heart	8.16 +-1.34	8.37 +-1.62	9.47 +-1.73	9.92 +-1.55	8.70 +-0.83
Body Wts (Kgs)	3.19 *+-0.37	3.66 +-0.62	4.15 +-0.60	4.36 +-0.36	4.11 +-0.34

* Significantly different from control at the 0.05 level of probability.

APPENDIX S

90-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
CLINICAL CHEMISTRY - MALE RABBITS

Dosage Predicted (Actual)	Alk. Phos IU/L	SGOT IU/L	SGPT IU/L	Glucose IU/L	T. Bili Mg/DL	Bun Mg/DL	Tot. LDH IU/L	Tot. Prot G/DL	Cholesterol IU/L	Calcium Mg/DL	CPK IU/L	Pro-Time Sec.
250 Mg/Kg (263.1)	71.20 +-9.50	27.50 +-22.70	50.50 +-35.32	153.20 +-13.81	0.20 +-0.05	20.65 +-2.75	59.62 +-36.42	6.90 +-0.59	34.77 +-11.89	16.48 +-1.27	485.09 +-248.74	6.1 +-0.3
50 Mg/Kg (48.3)	61.70 +-14.35	20.80 +-3.12	33.90 +-17.20	151.72 +-19.73	0.20 +-0.00	16.70 +-4.49	48.35 +-19.18	6.60 +-0.61	34.49 +-16.95	15.75 +-1.17	477.17 +-81.00	6.3 +-0.1+
25 Mg/Kg (24.9)	57.20 +-22.92	24.10 +-11.99	39.60 +-16.77	152.26 +-10.93	0.20 +-0.09	19.60 +-2.39	46.69 +-32.36	7.00 +-0.98	45.90 +-21.68	16.49 +-2.30	600.72 +-81.82	6.4 +-0.3
Ethylacetate (250 Mg/Kg)	107.30 +-42.06	20.90 +-5.57	34.70 +-12.36	151.77 +-11.03	0.30 +-0.08	16.60 +-2.09	36.09 +-9.75	6.40 +-0.59	36.73 +-15.08	15.44 +-0.84	526.26 +-101.30	6.0 +-0.2
Control	70.30 +-14.84	16.60 +-3.77	31.30 +-9.70	147.00 +-14.40	0.20 +-0.13	16.10 +-2.82	37.47 +-5.87	6.60 +-0.64	26.43 +-14.31	16.23 +-1.44	497.28 +-158.92	6.1 +-0.2

Alk.Phos - Alkaline Phosphatase
SGOT - Serum Glutamic Oxaloacetic Transaminase
SGPT - Serum Glutamic Pyruvic Transaminase
Glucose
T. Bili - Total Bilirubin
Bun - Blood Urea Nitrogen
Tot. LDH - Total Lactic Dehydrogenase
Tot. Prot. - Total Protein
Cholesterol
CPK - Creatine Phosphokinase
Prothrobin Times
CA - Calcium

APPENDIX T

90-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
CLINICAL CHEMISTRY - FEMALE RABBITS

Dosage Predicted (Actual)	Alk.Phos IU/L	SGOT IU/L	SGPT IU/L	Glucose IU/L	T.Bili Mg/DL	Bun IU/L	Tot.LDH IU/L	Tot.Prot. G/DL	Cholesterol IU/L	CPK IU/L	Pro-Times Sec.
150 Mg/Kg (158.9)	79.30 +-25.90	6.83 +-0.85	26.82 +-6.87	141.75 +-7.79	0.14 +-0.01	26.30 +-2.42	51.60 +-19.64	6.40 +-0.22	58.75 +-8.63	571.05 +-310.73	6.32 +-0.10
50 Mg/Kg (53.4)	70.94 +-63.01	11.61 +-1.38	39.00 +-12.11	134.17 +-13.92	0.15 +-0.04	19.34 +-4.69	46.84 +-22.91	6.13 +-0.27	55.31 +-23.29	345.70 +-65.80	6.00 +-0.25
25 Mg/Kg (27.3)	94.39 +-102.6	11.09 +-3.52	34.04 +-14.94	143.30 +-12.26	0.17 +-0.07	22.67 +-3.62	56.31 +-28.00	6.32 +-0.23	60.65 +-10.90	407.44 +-18 50	6.30 +-0.42
Ethylacetate (250 Mg/Kg)	65.25 +-20.90	11.39 +-3.50	35.44 +-5.54	147.14 +-5.24	0.10 +-0.02	21.21 +-1.91	33.21 +-8.37	6.07 +-0.42	55.04 +-20.12	290.89 +-91.88	6.26 +-0.24
Control	78.18 +-31.98	11.24 +-4.00	30.38 +-12.07	150.40 +-10.54	0.12 +-0.02	23.34 +-2.79	55.12 +-39.98	6.45 +-0.61	52.55 +-18.55	276.42 +-71.81	6.20 +-0.23

Alk.Phos - Alkaline Phosphatase
SGOT - Serum Glutamic Oxaloacetic Transaminase
SGPT - Serum Glutamic Pyruvic Transaminase
Cholesterol
Glucose
T. Bili - Total Bilirubin
Bun - Blood Urea Nitrogen
Tot. LDH - Total Lactic Dehydrogenase
Tot. Prot. - Total Protein
Prothrobin Times
CPK - Creatine Phosphokinase

APPENDIX U

90-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
HEMATOLOGY - FEMALE RABBITS

Dosage Predicted (Actual)	RBC 10/µL	HCT %	MCV fl	WBC 10/µL	HGB g/dl	MCH pg	MCHC g/dl	Heterophiles %	Lymphocytes %	Monocytes %
150 Mg/Kg (158.9)	5.30 *+-0.36	34.47 *+-1.95	65.12 +-1.63	7.62 +-1.56	11.42 *+-0.51	21.60 +-0.82	33.15 +-0.51	31.25 +-9.57	67.50 +-9.11	1.25 +-0.5
50 Mg/Kg (53.4)	5.50 +-0.58	35.45 +-3.03	64.57 +-2.32	9.80 +-1.72	11.95 +-1.13	21.75 +-1.28	33.70 +-1.05	47.00 +-15.77	52.00 +-14.72	2.00 +-0.00
25 Mg/Kg (27.3)	6.18 +-0.49	41.26 +-3.01	66.88 +-3.70	8.20 +-2.98	13.86 +-1.04	22.48 +-1.35	33.58 +-0.33	36.00 +-11.20	63.40 +-11.15	1.00 +-0.00
Ethylacetate (250 Mg/Kg)	6.04 +-0.66	39.90 +-3.10	66.29 +-2.24	9.71 +-1.87	13.36 +-1.10	22.14 +-0.70	33.43 +-0.27	34.57 +-8.68	64.57 +-8.56	1.00 +-0.00
Control	6.24 +-0.63	40.64 +-4.61	64.96 +-1.68	9.92 +-1.81	13.52 +-1.44	21.66 +-0.63	33.34 +-0.19	33.00 +-5.00	66.60 +-5.32	1.00 +-0.00

* Statistical significance at the p >0.05 level.

RBC - Red Blood Cells
HGB - Hemoglobin
HCT - Hematocrit
MCV - Mean Cell Volume
MCH - Mean Cell Hemoglobin
MCHC - Mean Cell Hemoglobin Concentration
WBC - White Blood Cell

APPENDIX V

90-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
HEMATOLOGY - MALE RABBITS

Dosage Predicted (Actual)	RBC 10/µL	HCT %	MCV fl	WBC 10/µL	HGB g/dl	MCH pg	MCHC g/dl	Heterophiles %	Lymphocytes %	Monocytes %
250 Mg/Kg (263.1)	5.34 *+-0.55	35.99 *+-3.16	67.56 +-2.48	8.86 +-2.46	12.02 *+-1.07	22.59 +-1.04	33.42 +-0.65	41.87 +-13.88	57.37 +-14.30	1.20 +-0.45
50 Mg/Kg (48.3)	6.02 +-0.69	39.22 +-3.95	65.20 +-1.82	9.62 +-1.72	13.27 +-1.20	22.07 +-0.74	33.87 +-0.43	36.75 +-10.93	63.25 +-10.93	1.00 +-0.00
25 Mg/Kg (24.9)	6.18 +-0.22	40.18 +-2.38	63.98 ++0.73	11.40 +-2.96	13.50 +-0.86	21.84 +-0.78	33.60 +-0.16	34.80 *+-9.63	63.80 *+-9.88	1.75 +-0.5
Ethylacetate (250 Mg/Kg)	6.09 +-0.21	40.46 +-2.00	66.46 +-1.30	9.37 +-1.82	13.74 +-0.74	22.59 +-0.54	33.94 +-0.38	36.86 +-15.99	62.57 +-15.74	1.00 +-0.00
Control	6.50 +-0.42	42.37 +-2.74	65.20 +-2.02	10.15 +-1.84	14.32 +-0.90	22.05 +-0.68	33.82 +-0.15	54.25 +-10.21	45.75 +-10.21	0.00 +-0.00

* Statistical significance at the p >0.05 level.

RBC - Red Blood Cells
HGB - Hemoglobin
HCT - Hematocrit
MCV - Mean Cell Volume
MCH - Mean Cell Hemoglobin
MCHC - Mean Cell Hemoglobin Concentration
WBC - White Blood Cell

APPENDIX W

RABBIT 90-DAY DERMAL APPLICATION
DANPE
STUDY NO. 75-51-0809-91
FEMALE BRAIN TO ORGAN WEIGHT RATIOS (GMS)

% OF BRAIN WEIGHT

Dosage Predicted (Actual)	250 Mg/Kg (263.1)	50 Mg/Kg (48.3)	25 Mg/Kg (24.9)	Ethylacetate (250)	Cage Cont (0)
Liver	1309.33 +-201.33	1156.39 +-224.90	1340.64 +-372.53	1431.88 +-466.08	1285.53 +-278.21
Kidney	197.92 +-19.33	189.45 +-24.56	193.76 +-23.71	227.59 +-52.79	195.73 +-20.98
Spleen	14.66 +-7.37	17.61 +-8.50	18.40 +-3.50	18.58 +-7.75	18.13 +-5.55
Heart	79.00 +-15.74	71.54 *+-10.71	79.68 +-13.21	86.97 +-17.39	81.21 +-7.63
Ovaries	1.82 *+-0.60	2.18 *+-0.81	4.16 +-2.41	5.73 +-4.59	5.57 +-2.77
Adrenal	4.02 +-0.84	3.50 *+-0.79	4.01 +-0.69	4.79 +-1.31	4.25 +-0.65

* Significantly different from control at the 0.05 level of probability.

APPENDIX X

RABBIT 90-DAY DERMAL
DANPE
STUDY NO. 75-51-0809-91
MALE BODY TO ORGAN WEIGHT RATIOS

% OF BODY WEIGHT

Dosage Predicted (Actual)	250 Mg/Kg (263.1)	50 Mg/Kg (48.3)	25 Mg/Kg (24.9)	Ethylacetate (250)	Cage Cont (0)
Liver	3.34 +-0.43	3.11 +-0.36	3.20 +-0.48	3.21 +-0.38	3.00 +-0.26
Kidney	0.58 *+-0.04	0.54 +-0.11	0.49 +-0.07	0.48 +-0.07	0.45 +-0.05
Heart	0.26 *+-0.03	0.23 +-0.03	0.23 +-0.04	0.23 +-0.03	0.21 +-0.01
Spleen	0.04 +-0.01	0.03 +-0.01	0.04 +-0.01	0.03 +-0.01	0.04 +-0.01
Testes	0.04 *+-0.01	0.05 *+-0.01	0.06 *+-0.02	0.14 +-0.03	0.15 +-0.02
Brain	0.31 *+-0.04	0.28 *+-0.03	0.25 +-0.04	0.23 +-0.02	0.25 +-0.02

* Significantly different from control at the 0.05 level of probability.